A common gut fungus worsens infection with the food-borne bacterium *Salmonella*

In an intricate interaction spanning domains of life, the bacterium *Salmonella* hijacks the yeast *Candida* to make it produce and release the amino acid arginine in the gut. Arginine increases the virulence of *Salmonella* and downregulates the host's immune response to *Salmonella* infection, leading to more-severe disease.

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The problem

Communities of microorganisms in the gut, called the microbiota, are crucial for human health. Research has focused mainly on bacteria, which are the most numerous microbes in the gut, but fungi are associated with many diseases, including inflammatory bowel disease[1]. Knowledge of how fungi modulate disease is limited, however.

We wanted to show how the fungi that live in the gut can influence infection by a pathogenic gut microbe. We used the bacterium *Salmonella* Typhimurium, a food-borne bacterial pathogen that causes inflammation in the gut and that can spread beyond the gut in vulnerable people. The bacterial microbiota is known to modulate *Salmonella* disease[2], but whether and how fungi can affect it has been unclear.

The discovery

We were initially interested in how the presence of *Salmonella* changes the relative abundance of fungi in the gut. *Salmonella* causes inflammation, so we expected to find changes that depend on how well different fungi can tolerate inflammatory conditions. We found that the population of *Candida albicans*, a common fungus often found in the gut[3], increased in most mice after *Salmonella* infection. The mice with *Candida* developed more-severe illness from *Salmonella* than did those without yeast in their gut. In these co-infected mice, more *Salmonella* escaped the gut environment, spreading to other organs, such as the liver and spleen (Fig. 1a), than in mice infected with only *Salmonella*. To determine the mechanism, we cultured *Salmonella* and *Candida* together with epithelial cells (the cells that line the gut wall). Using RNA sequencing and amino acid metabolomics, we generated several hypotheses and tested them in various mouse models.

We discovered an unexpectedly complex interaction between *Salmonella*, *Candida* and the host mouse. *Salmonella* bound to *Candida* using hair-like appendages called type 1 fimbriae. *Salmonella* then used a needle-like apparatus called the type 3 secretion system (T3SS) to inject proteins into gut epithelial cells. We found that it also used this system to interact with, and elicit responses in, *C. albicans* (Fig. 1b). One of the proteins delivered by the T3SS, known as SopB, caused a marked increase in biosynthesis of the amino acid arginine in *Candida*. Arginine released from *Candida* had two initial effects: it increased the expression of *Salmonella* genes associated with disease severity (Fig. 1b), leading to increased invasion into gut epithelial cells, and it dampened the immune response of mice to infection. These two effects contributed to an increase in *Salmonella* numbers in the gut and helped the bacteria spread to other organs.

The implications

Candida is found in the gut of most people[3], so it is present in most cases of *Salmonella* infection. It might worsen infections with *Salmonella* in humans, in a way similar to the effect that we observed in mice. Our findings might be particularly relevant to vulnerable populations, such as immunocompromised individuals, who are given antibiotics to treat *Salmonella* infections. Although the antibiotics kill the bacteria, they also enable the *Candida* population to expand, potentially worsening the *Salmonella* infection.

The presence or absence of *Candida* is not currently assessed when clinicians suspect intestinal infection. We therefore do not yet know whether *Candida* does indeed worsen *Salmonella* infections in humans.

We hope that researchers will investigate whether our findings in mice translate to humans. One clinical study found that the presence of *Candida* increases the recurrence of *Salmonella* infections[4], but more studies are needed to determine how *Candida* affects the severity of infections. We hope to investigate whether *C. albicans* is the only yeast that worsens *Salmonella* infections, whether other gut pathogens adopt similar strategies to *Salmonella*, and whether the presence of *Salmonella* brings any benefit to the yeast.

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EXPERT OPINION

"This study sheds light on an understudied aspect of the microbiome, the mycobiome, and its effect on disease processes. The discovery that *Candida* and *Salmonella* interact metabolically through arginine cross-feeding is thus timely and exciting, and markedly extends our knowledge of the gut microbiome. Most exciting to me is the first evidence, to my knowledge, that *Salmonella* uses a type 3 secretion system effector to manipulate non-mammalian cells — specifically, *Candida*." (CC BY 4.0)

Sebastian Winter is at the University of California, Davis, Davis, California, USA.

FIGURE

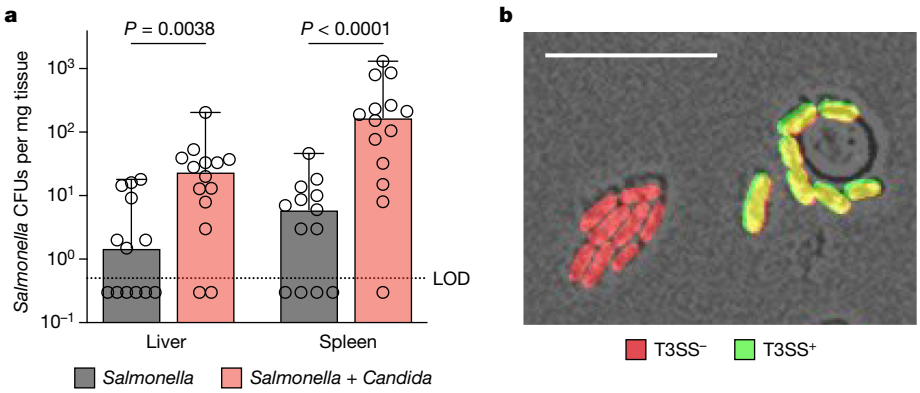

Figure 1 | Interactions of *Salmonella* bacteria with the yeast *Candida*. **a**, The burden of *Salmonella* in the liver and spleen of mice 48 hours after infection with both *Salmonella* and *Candida* was greater than in mice infected with only *Salmonella*. Each circle represents an individual mouse. CFUs, colony-forming units; LOD, limit of detection. **b**, Fluorescence image of *Salmonella* expressing a red fluorescent protein and a green fluorescent version of a protein in a needle-like apparatus called the type 3 secretion system (T3SS), which injects proteins into other cells. A *Candida* cell (round) is visible in bright field. There was an increase in *Salmonella* T3SS-positive cells in the presence of *Candida*, specifically in cells close to *Candida*. Scale bar, 10 micrometres. Jaswal, K. *et al.*/*Nature* (CC BY 4.0).

BEHIND THE PAPER

Our lab is generally interested in the role of fungi during bacterial infections. However, we did not set out to study the interaction of two model pathogens in the gut. It was merely fortuitous for our research that *Salmonella* interacted with *Candida*, a model yeast pathogen, because it opened a wealth of tools to use for mechanistic research. We already had, or were able to acquire, *Salmonella* strains, and the lab of co-author Brian Peters provided us with *Candida* strains and expertise. At first, we could not explain the reduced inflammation in the gut during co-infection, and this stopped part of the project for a whole year. Only after we found that arginine is produced during co-culture of *Salmonella* and *Candida* did this finding make sense, and it enabled us to continue research on this arm of the project.

J.B.

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FROM THE EDITOR

Pathogenic microbes in the intestine often use effector proteins to manipulate their host and increase their virulence. This paper presents a conceptual twist in that the pathogen exploits a commensal fungus in the same niche to amplify its virulence.

Editorial team, *Nature*